

Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

Gustavo M. Borrajo-Calleja, Vincent Bizet, and Clément Mazet*

Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva, Switzerland

S Supporting Information

ABSTRACT: A novel enantioselective Pd-catalyzed intermolecular carboetherification of dihydrofurans is reported. The in situ generation of chiral bis-phosphine mono-oxide ligands is crucial, and a general catalytic system has been identified based on this approach. It provides access to a variety of fused tetrahydrofurobenzofurans in consistently high yield and enantiomeric excess.

The 2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran scaffold is frequently found in biologically active compounds such as aspersversin A or aflatoxin B₂, a potent mutagen (Figure 1A).¹

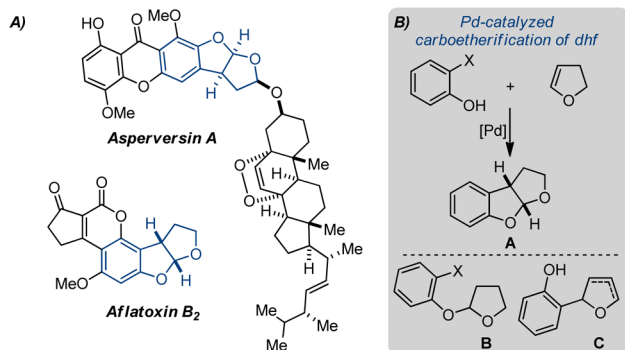


Figure 1. Biologically active tetrahydrofurobenzofurans (A) and proposed intermolecular carboetherification of dihydrofuran (B).

Nonetheless, direct access to this synthetic motif remains particularly challenging, and only a handful of enantioselective approaches have been disclosed.² We envisaged that the effective development of a Pd-catalyzed enantioselective intermolecular carboetherification starting from 2,3-dihydrofurans (dhf) and 2-halophenol derivatives would provide direct access to this pattern (A on Figure 1B). Despite recent and remarkable advances in the field, such a process is notably absent from the current portfolio of carboetherification of alkenes.³ Importantly, most reported examples proceed via intramolecular reactions, and their enantioselective variants are still scarce.⁴ We anticipated that the successful realization of this goal would require circumventing the formation of the competing α -etherification and Heck products B and C that may form under typically basic cross-coupling reaction conditions.^{5,6}

Here, we describe the first examples of enantioselective intermolecular Pd-catalyzed syn-carboetherifications of olefins affording fused tetrahydrofurobenzofurans in good yield and excellent level of enantiomeric excess.

In our exploratory experiments, we investigated the coupling between 2,3-dihydrofuran **1a** and 2-bromophenol **2a** using CPhos (**L1**), a prototypical monodentate biarylphosphine ligand (Table 1, entry 1).⁷ After a rapid survey of various reaction

Table 1. Reaction Optimization^a

The reaction scheme shows the synthesis of 3a, 4a, and 5a from 1a and 2a. The reaction conditions are: Pd₂(dba)₃ (2.5 mol%), Ligand (5.0 mol%), *t*BuONa (1.5 equiv.), Toluene (0.2 M).

entry	ligand	<i>t</i> (h)	<i>T</i> (°C)	yield (%) ^b
1	L1 (CPhos)	24	110	56
2	L2 (DavePhos)	24	110	nr
3	L3 (XPhos)	24	110	nr
4	L4 (JohnPhos)	24	110	nr
5	L5 (<i>t</i> BuDavePhos)	24	110	45
6	L6 (<i>t</i> BuXPhos)	24	110	68
7	L7 (TrixiePhos)	24	110	36
8	L8 (RuPhos)	24	110	73
9	L8 (RuPhos)	4	50	traces
10	L8 (RuPhos)	6	110	56 ^c
11	L8 (RuPhos)	4	80	73

^aReaction conditions: **1** (1.0 mmol), **2a** (0.2 mmol). ^bDetermined after purification by column chromatography. ^cUsing 2-chlorophenol.

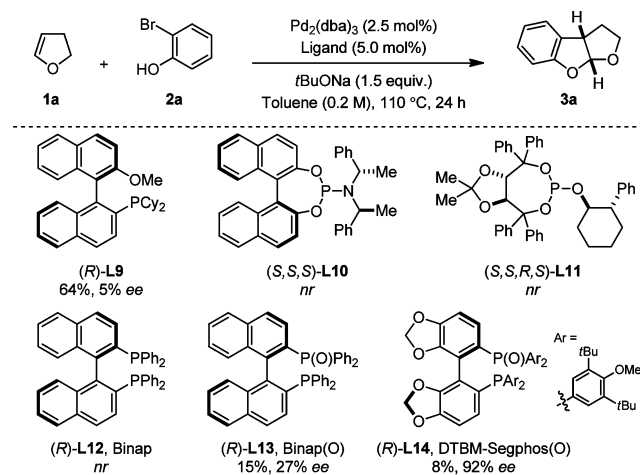
parameters, we were delighted to find that **3a** could be formed exclusively and isolated in 56% yield after heating at 110 °C a toluene solution for 24 h using *t*BuONa (1.5 equiv) and Pd₂(dba)₃ (2.5 mol %). In an attempt to improve reactivity, additional Buchwald-type phosphine ligands were evaluated next. Whereas **L2** (DavePhos), **L3** (XPhos), and **L4** (JohnPhos) did not prove competent for this transformation, the sterically demanding **L5** (*t*BuDavePhos), **L6** (*t*BuXPhos), and **L7** (TrixiePhos) all afforded **3a** in moderate to acceptable yield

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(45%, 68%, and 36% yields, respectively; Table 1, entries 2–7). Satisfactorily, with L8 (RuPhos), the yield was improved to 73%. This performance could be maintained even when the reaction was performed at lower temperature and in a much reduced time (80 °C, 4 h; Table 1, entry 11). Of note, products 4a and 5a were only detected when other bases or ligands were employed. Higher yields were obtained using a 5:1 stoichiometry between 2,3-dhf 1a and 2-bromophenol 2a (see Supporting Information (SI) for details).

We next turned to the development of an enantioselective version of this intermolecular carboetherification reaction using the same model reaction between 1a and 2a (Table 2).

Table 2. Chiral Ligand Survey^a

^aReaction conditions: 1a (1 mmol), 2a (0.2 mmol). Yields of isolated products after purification. Enantioselectivity determined by HPLC using a chiral column.

Reasoning that the MOP-type ligands originally designed by Hayashi may constitute closely related structural analogues of RuPhos, ligand L9 was evaluated first.⁸ After 24 h at 110 °C, 3a was isolated in reasonable yield but in almost racemic form (64% yield, 5% ee). The less basic Binol-based phosphoramidite ligand (L10) and Taddol-based phosphite ligand (L11), which were recently found to be suitable ligands in a related intramolecular carboalkoxylation of alkenes, only generated traces of the carboetherification product 3a along with minute amount of 5a.^{4g} Interestingly, whereas Binap (L12) was ineffective in the carboetherification reaction, its corresponding monoxide Binap(O) (L13) delivered 3a in 15% yield and 27% ee. These results are consistent with the notion that Binap(O) is a hemilabile ligand that behaves temporarily as a monodentate chiral phosphine ligand.^{9–11} With another member of this ligand class, DTBM-Segphos(O) (L14), 3a was still obtained in modest yield but in excellent enantiomeric excess (92% ee).¹²

To ensure rapid identification of a lead structure, we next focused on the development of a protocol that would enable in situ generation of chiral bis-phosphine mono-oxide ligands (BPMO) starting from their commercially available bisphosphine precursors (Table 3). Our approach was inspired by the seminal contributions of Ozawa and Hayashi who demonstrated that Binap(O) could be generated in situ under basic conditions using Pd(OAc)₂ and a controlled amount of added water.¹³ Very recent reports from Li and Belk and Eastgate and Blackmond are also in line with this approach.^{14,15}

Table 3. Effect of Added Water and Final Evaluation of Chiral Ligands^a

Reaction scheme for Table 3: 1a + 2a $\xrightarrow[\text{Toluene (0.2 M), 110 }^\circ\text{C, 24 h}]{[\text{Pd}] (5.0 \text{ mol}\%), \text{Ligand (5.0 mol}\%), \text{tBuONa (1.5 equiv.)}}$ 3a

Ligand structures:

- (S)-L15: Ar = tBu
- (S)-L16: Ar = tBu, NMe₂
- (S)-L17: Ar = OMe, OMe
- (S)-L18: Ar = tBu, OMe

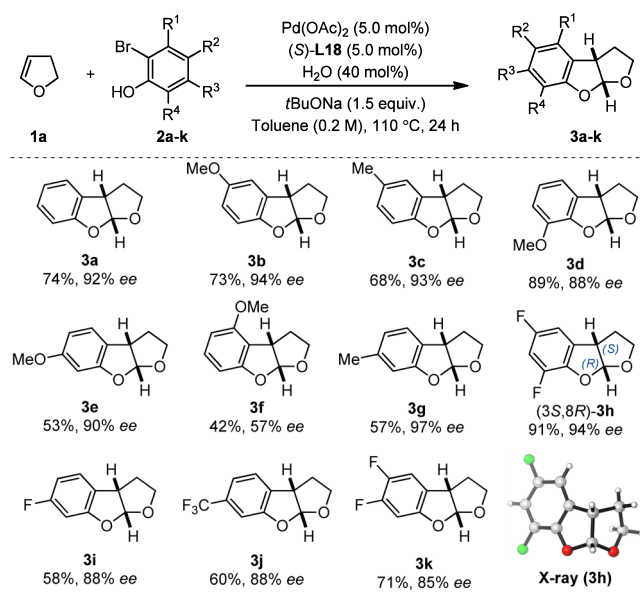
entry	ligand (5 mol %)	[Pd] (5 mol %) ^b	H ₂ O (mol %)	yield (%) ^c	ee (%) ^d
1	DTBM-Segphos	Pd2(dba)3	–	nr	nd
2	L14	Pd2(dba)3	–	8	92
3	DTBM-Segphos	Pd(OAc)2	–	16	90
4	DTBM-Segphos	Pd(OAc)2	20	31	83
5	DTBM-Segphos	Pd(OAc)2	40	40	85
6	DTBM-Segphos	Pd(OAc)2	60	35	81
7	L15	Pd(OAc)2	40	76	90
8	L16	Pd(OAc)2	40	66	90
9	L17	Pd(OAc)2	40	31	65
10	L18	Pd(OAc)2	40	74	92

^aReaction conditions: 1a (1 mmol), 2a (0.2 mmol). ^bConcentration in Pd. ^cAfter purification by chromatography. ^dDetermined by HPLC using a chiral column.

The model reaction between 1a and 2a was therefore carried out using the bisphosphine ligand DTBM-Segphos (5 mol %), Pd(OAc)₂ (5 mol %), and variable amounts of water (0–60 mol %). Although reactivity was observed in the absence of water, the optimal result was obtained when 40 mol % of water was added to the mixture (entry 3–6). The yield in carboetherification product 3a was significantly improved, while the erosion in enantioselectivity remained acceptable. Subsequently, a range of commercially available bisphosphines was evaluated (see SI for details). From this screening, it clearly appeared that ligands of the Biphep family (L15–18) with sterically demanding and electron-rich aryl substituents were particularly well-suited candidates (Table 3, entries 7–10).¹² Gratifyingly, with L18 the carboetherification product 3a was isolated in 74% yield and 92% ee.

The scope of the reaction was delineated with L18 using the protocol for in situ mono-oxidation of the ligand (Table 4). Overall, both electron-rich and electron-deficient 2-bromophenols participated efficiently in the syn-carboetherification of 2,3-dihydrofuran 1a, delivering the product in consistently good yield and high levels of enantioselectivity (10 examples: 3a–e, g–k 53–91% yield; 85–97% ee). Interestingly, an electron-withdrawing or an electron-donating group can be placed indifferently in para position with respect to the bromine atom or the –OH functionality without noticeable effect on the reaction outcome. However, when 2-bromo-3-methoxyphenol 2f was employed, both the reactivity and the enantioselectivity were affected significantly (3f: 42% yield, 57% ee).

Substituted dihydrofurans are notoriously more difficult to engage in cross-coupling reactions than their unsubstituted counterparts.¹⁸ Therefore, the influence of substitution on various positions of the dihydrofuran ring was investigated next (Figure 2). When 5-methyl-2,3-dihydrofuran 1b was subjected to the optimized reaction conditions, increasing the catalyst loading to 10 mol % was required to maintain a reasonable level of reactivity. The corresponding fused tetrahydrofurobenzofurans

Table 4. Scope of the Enantioselective Intermolecular Carboetherification of 2,3-Dihydrofuran^a

^aReaction conditions: **1a** (1 mmol), **2a–k** (0.2 mmol). Yields of isolated products after purification. Enantioselectivity determined by HPLC or GC using a chiral column. Absolute configuration of all products is as shown and was assigned by analogy with the X-ray crystallography analysis of (3*S*,8*R*)-**3h**.¹⁶

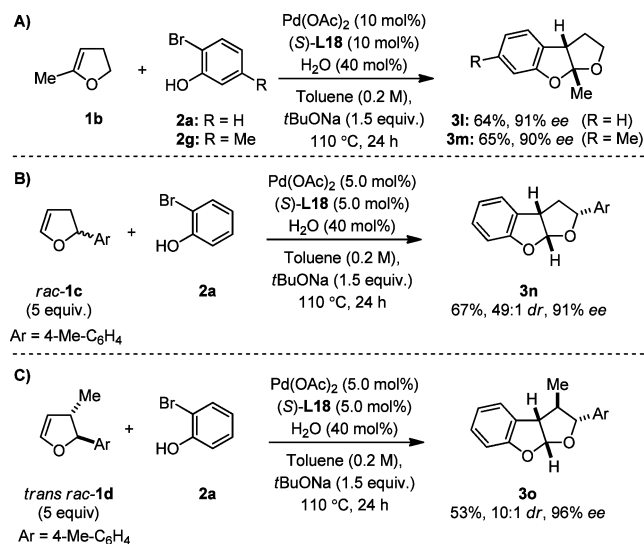


Figure 2. Variation of the dihydrofuran structure. Reaction conditions: **1b–d** (1 mmol), **2a**, or **2g** (0.2 mmol). Yields of isolated product. Enantioselectivity determined by HPLC or GC using a chiral column. Diastereomeric ratio measured by ¹H NMR of the crude reaction mixture. (A) Using 5-methyl-2,3-dihydrofuran **1b**. (B) Using *rac*-2-(*p*-tolyl)-2,3-dihydrofuran **1c**. Recovered **1c**: 37% yield, 12% ee, yield based on *rac*-**1c**. (C) Using *rac*-*trans*-3-methyl-2-(*p*-tolyl)-2,3-dihydrofuran **1d**. Recovered **1d**: 64% yield, 8% ee, yield based on *rac*-**1d**.¹⁷

3l–m with a fully substituted congested acetal carbon stereocenter were isolated in good yields and excellent levels of enantioselectivity (Figure 2A). Interestingly, 2-(*p*-tolyl)-2,3-dihydrofuran **1c**—obtained from an independent Heck cross-coupling reaction^{5,19}—also proved a competent partner delivering **3n** as a single diastereoisomer in 67% yield and 91% ee (Figure 2B). More remarkably, *trans*-3-methyl-2-(*p*-tolyl)-2,3-

dihydrofuran **1d**^{19,20} afforded the corresponding carboetherification product **3o** with four contiguous stereocenters in 53% yield, 10:1 dr, and 96% ee (Figure 2C). Of note, an optically active tetrahydrofurobenzofurans with such a level of stereochemical complexity would certainly be difficult to prepare by conventional methods.²¹

In conclusion, we have developed a very general and unprecedented enantioselective Pd-catalyzed intermolecular syn-carboetherification of dihydrofurans using in situ generated chiral bis-phosphine mono-oxide ligands. The method gives readily access to synthetically relevant and stereochemically complex fused tetrahydrofurobenzofurans in high yield, diastereoselectivity, and enantioselectivity. Further mechanistic studies into the origin of the reactivity and selectivity of this catalytic system are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02158.

Experimental details and data and X-ray data for compound **3h** (CCDC 1455966) (PDF)

Crystallographic data (CIF)

Crystallographic data (CIF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*clement.mazet@unige.ch

Notes

The authors declare no competing financial interest.

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